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(71) Applicant : **LOUISIANA STATE UNIVERSITY AGRICULTURAL AND MECHANICAL COLLEGE**
Systems Building, Room 107, University Station
Baton Rouge, Louisiana 70803 (US)

(72) Inventor : **Cincotta, Anthony**
134A Elm Street
Andover, Massachusetts 01810 (US)
Inventor : **Meier, Albert**
6165 Chandler Drive
Baton Rouge, Louisiana 70808 (US)

(74) Representative : **Crampton, Keith John Allen et al**
D. YOUNG & CO. 10 Staple Inn
London WC1V 7RD (GB)

(54) Dopamine agonists for treating type II diabetes.

(57) A process for the long term modification and regulation of lipid metabolism – generally to reduce obesity, insulin resistance, and hyperinsulinemia or hyperglycemia, or both (these are the hallmarks of noninsulin dependent, or Type II diabetes) -- by administration (i.e., by feed or injection into the bloodstream) to a vertebrate, animal or human, of a dopamine agonist, e.g., bromocriptine. Administration of the bromocriptine is made over a limited period at a time of day dependent on the normal circadian rhythm of fat and lean members of a similar species. Decreases in body fat deposits result by treatment of an obese species on a daily timed sequence based on circadian rhythms of the peak prolactin, or peak prolactin and peak glucocorticosteroid, blood level established for lean members of a similar species. Insulin resistance, and hyperinsulinemia and hyperglycemia, or both, can also be controlled in humans on a long term basis by treatment corresponding to that of the treatment for obesity. The short term daily injections reset hormonal timing in the neural centers of the brain to produce long term effects.

EP 0 440 333 A2

PROCESS FOR THE LONG TERM REDUCTION OF BODY FAT STORES, INSULIN RESISTANCE, HYPERINSULINEMIA AND HYPOGLYCEMIA IN VERTEBRATES

This invention relates to a process for the reduction in vertebrates, animals or humans, of body fat stores, and reduction of insulin resistance, hyperinsulinemia, which is often associated with insulin resistance, and hyperglycemia, or reduction of plasma glucose ; pathologies characteristic of the onset of noninsulin dependent, or Type II diabetes.

Diabetes, one of the most insidious of the major diseases, adversely affects the way the body uses sugars and starches which, during digestion, are converted into glucose. Insulin, a hormone produced by the pancreas, makes the glucose available to the body's cells for energy. In muscle, adipose (fat) and connective tissues, insulin facilitates the entry of glucose into the cells by an action on the cell membranes. The ingested glucose is normally burned in the liver to CO_2 and H_2O (50%) ; to glycogen (5%), and to fat (30-40%), which is stored in fat depots. Fatty acids are circulated, returned to the liver and metabolized to ketone bodies for utilization by the tissues. The fatty acids are also metabolized by other organs, fat formation being a major pathway for carbohydrate utilization. The net effect of insulin is to promote the storage and use of carbohydrates, protein and fat. Insulin deficiency is a common and serious pathologic condition in man. In Type I diabetes the pancreas produces little or no insulin, and insulin must be injected daily for the survival of the diabetic. In Type II diabetes the pancreas produces some insulin, but the amount of insulin is insufficient, or less than fully effective due to cellular resistance, or both. In either form there are widespread abnormalities, but the fundamental defects to which the abnormalities can be traced are (1) a reduced entry of glucose into various "peripheral" tissues and (2) an increased liberation of glucose into the circulation from the liver (increased hepatic glucogenesis). There is therefore an extracellular glucose excess and an intracellular glucose deficiency which has been called "starvation in the midst of plenty". There is also a decrease in the entry of amino acids into muscle and an increase in lipolysis. Thus, these results, as a result of the diabetic condition, elevated levels of glucose in the blood, and prolonged high blood sugar is indicative of a condition which will cause blood vessel and nerve damage. Obesity, or excess fat deposits, it is believed may trigger the onset of diabetes by increasing cellular resistance to insulin. Prior to the onset of diabetes, the pancreas of the obese are taxed to produce additional insulin ; but eventually, perhaps over several years, insulin productivity falls and diabetes results. Reduction of body fat can improve insulin production, and it is thought avoid cellular insensitivity to insulin.

Obesity, and insulin resistance, the latter of which is generally accompanied by hyperinsulinemia or hyperglycemia, or both, are hallmarks of Type II diabetes. Whereas controlled diet and exercise can produce modest results in the reduction of body fat deposits, no effective treatment has been found for controlling either hyperinsulinemia, or insulin resistance. Hyperinsulinemia is a higher-than-normal level of insulin in the blood. Insulin resistance can be defined as a state in which a normal amount of insulin produces a subnormal biologic response. In insulin-treated patients with diabetes, insulin resistance is considered to be present whenever the therapeutic dose of insulin exceeds the secretory rate of insulin in normal persons. Insulin resistance is also found in the setting defined by higher-than-normal levels of insulin -- i.e., hyperinsulinemia -- when there is present normal or elevated levels of blood glucose. Despite decades of research on these serious health problems, the etiology of obesity and insulin resistance is unknown.

The present invention is characterized as a process, or method, for the regulation of lipid metabolism to produce long term, lasting, and permanent effects by the administration of timed daily dosages to a vertebrate, animal or human, of a dopamine agonist, or prolactin inhibitor, such as L-dopa and various ergot-related compounds. The dosages are continued on a daily basis for a period sufficient to reset the phase oscillation of the prolactin rhythm, or oscillations of both the prolactin and glucocorticosteroid rhythms which are expressions of the prolactin and glucocorticosteroid neural oscillations, respectively. The phase relationship of the prolactin oscillation, and preferably both neural oscillations are modified and reset such that, on cessation of the daily dosages of the dopamine agonist, or prolactin inhibitor, the lipid metabolism of the animal, or human, continues over a long term period, if not permanently, at the altered metabolic setpoint, or setpoints.

A dopamine agonist, or prolactin inhibiting compound is administered to the vertebrate, animal or human, orally or by subcutaneous or intramuscular injection into the bloodstream. Thus, a prolactin-inhibiting compound, preferably an ergot-related prolactin-inhibiting compound, is administered to a subject exhibiting any one or more of the symptoms desirable of change, e.g., obesity, insulin resistance, hyperinsulinemia or hyperglycemia. Exemplary of prolactin-inhibiting, ergot related compounds are : 2-bromo-alpha-ergocryptine ; 6-methyl-8beta-carbobenzyloxy-aminomethyl-10alpha-ergoline ; 1,6-dimethyl-8beta-carbobenzyloxy-aminomethyl-10alpha-ergoline ; 8-acylaminoergolenes, such as 6-methyl-8alpha-(N-acyl)amino-9-ergolene and 6-methyl-8alpha-(N-phenylacetyl)amino-9-ergolene ; ergocornine ; 9,10-dihydroergocornine ; and D-2-halo-6-alkyl-8-substituted ergolines, e.g., D-2-bromo-6-methyl-8-cyanomethylergoline. Moreover, the non-toxic salts

of the prolactin-inhibiting ergot-related compounds formed from pharmaceutically acceptable acids are also useful in the practice of this invention. Bromocriptine, or 2-bromo-alpha-ergocryptine, has been found particularly useful in the practice of this invention.

In the treatment of an animal, or human subject, the stores of body fat can be depleted or increased, the treatments continued until the stores of body fat are stabilized at an optimum or near-optimum level dependent on the level of body fat stores desired in the subject, for time sufficient that on termination of the treatment the prolactin rhythm, and preferably both the prolactin and glucocorticosteroid rhythms, is reset to maintain on a long term basis the reduced, or increased, body weight stores. In humans, the objective is almost invariably to reduce body fat stores, and obesity. It has been established that a relationship exists between obesity and insulin resistance, and that obesity can lead to increased insulin resistance. Likewise, it has been established that the circadian rhythms of plasma prolactin and glucocorticosteroid concentrations, respectively, have important consequences in the regulation of body fat stores, and that the phase relationship between the prolactin and glucocorticosteroid levels, respectively, differ in lean and fat animals. In a fat animal prolactin will reach a peak level at a given hour of a 24 hour period (in a human usually near midday), and the prolactin level of a lean animal at another time of day (in a human usually during sleep). In a lean animal the glucocorticosteroids, e.g., cortisol, will peak during a 24 hour period at a given hour (generally at a time different from that of prolactin) ; in a human generally several hours after waking. Thus, the phase relations of the cortisol and prolactin rhythms differ in lean and fat animals. The peak periods of prolactin and glucocorticosteroid production, respectively, may differ to some extent between male and females of any given species. This being so, it has been found that daily dosages of a dopamine agonist, or prolactin inhibitor, given to an obese subject shortly after the normal time of day that the prolactin is at its peak in a lean subject of the same species and sex will produce a weight reduction in the obese subject. Such treatment will, if continued over a sufficient period, reset on a long term or permanent basis the phase of the neural oscillation for the prolactin rhythm, or the phases of the neural oscillations for both the prolactin and glucocorticosteroid rhythms in the obese individual to that present in a lean subject. The obese subject, on initiation of the treatment with the dopamine agonist, or prolactin inhibitor, will lose body fat stores, and the body fat deposits of the obese subject on continuation of the treatments on a daily basis will drop to and stabilize at that of a lean subject of the same species. On discontinuing the daily treatments, the rise and fall of the prolactin, or prolactin and glucocorticosteroid levels in the blood of the treated patient on a daily basis will correspond to that of a lean subject of the same species, and for a period of long duration. The effect of resetting the prolactin, or prolactin and glucocorticosteroid rhythms, in this manner also increases the sensitivity of the cells of the subject to insulin, reduces hyperinsulinemia or hyperglycemia, or both, and thus alters long term pathologies which are characteristics of the onset of Type II diabetes.

In treating vertebrates, generally, dosages of the dopamine agonist, or prolactin are given once a day on a daily basis, generally over a period ranging from about 10 days to about 90 days, at levels ranging from about 3 micrograms to about 100 micrograms, per pound of body weight, to reset the circadian plasma prolactin rhythm. In treating humans, the dopamine agonist, or prolactin inhibitor, is preferably given at dosage levels ranging from about 3 micrograms to about 20 micrograms, per pound of body weight. Such treatments over a period of about 30 days to about 60 days given an obese person daily just a short period after -- generally about 1 hour to about 4 hours thereafter, preferably from about 1 hour to about 2 hours thereafter – the prolactin concentration peaks in a lean person will modify and reset the lipid metabolism of the obese person to that of a lean person. Body fat deposits, inclusive of adipose, arterial wall and plasma fat, within the obese person will be reduced, levelled out and maintained after the treatments are discontinued at that of a lean person, over an extended period of time. A lean or obese person showing the effects of insulin resistance, or hyperinsulinemia and/or hyperglycemia, or both insulin resistance and hyperinsulinemia and/or hyperglycemia, treated with the dopamine agonist, or prolactin inhibitor, in the same manner as a person suffering with obesity, will become more sensitive to insulin (i.e., will have a lower insulin resistance), and the effects of hyperinsulinemia and/or hyperglycemia will be reduced on a long term basis. The injections of the dopamine agonist, or prolactin inhibitor, will thus reset the phase relations of the two neural oscillations and their multiple circadian expressions to alter metabolism on a long term basis, if not permanently. In other words, there will be as a result of the timed daily dosages of the dopamine agonist, or prolactin inhibitor, a long term reversal of the major pathologies generally associated with the development of Type II diabetes. The levels of body fat stores plasma insulin concentrations and insulin resistance, hyperglycemia, or all of these pathologies can be reduced on a long term basis by such treatment, or treatments, from the high levels often found in obese, hyperinsulinemic persons to that of the much lower and more desirable levels found in lean persons.

In terms of the human subject, "obesity can be defined as that body weight over 20 percent above the ideal body weight for a given population" (R. H. Williams, Textbook of Endocrinology, 1974, p. 904-916.). The time of day when the prolactin and glucocorticosteroid levels, respectively, will peak in the blood of humans during a day differs between obese subjects and lean subjects, and the peak in each type of subject can be readily

determined by measurement of the fat and lean specimens, as defined. In other animal species what constitutes obese and lean members, respectively, of a species can be readily determined by body weight patterns correlated with the prolactin and glucocorticosteroids levels, respectively, in the plasma of the lean and obese members, respectively. The levels differ between members of the different species, but among members of the same species there is close correlation between the prolactin and glucocorticosterone levels, respectively, at certain time of the day dependent on the obesity or leanness of a given specimen.

These and other features of the invention will be better understood by reference to the following information and data of experimental work with animals and humans. In the examples the terminology "LD" refers to the light/dark cycle, the first number following the expression LD refers to the hours of light, and the second to the hours of darkness in the cycle. Thus LD 14 :10 refers to a cycle having 14 hours of light and 10 hours of darkness, and the period of a day is expressed in terms of 2400 hours. The letter n refers to the number of animals in a group, "BW" designates body weight, g represents grams and "ug" is an expression of micrograms.

In the following example data are given which show the altered phase relationships of the circadian rhythms of plasma corticosteriod and prolactin concentrations in swine ; changes beneficial in the treatment of diabetics.

Example 1

Adult female pigs, six in number, were given bromocryptine implants (10 mg/pig/day) over a period of time while being subjected to daily periods of daylight and darkness (12 :12). A control group of six pigs were similarly treated to periods of daylight and darkness except that no bromocryptine was administered to the pigs of the control group. The period of darkness was from 1800 to 0600, and the period of daylight from 0600 to 1800. Daily tests were made of the blood of the pigs at four hour intervals over a 14 day period to determine the plasma cortisol level (ug/dl) and plasma prolactin level (ug/ml) of both groups. The average for each series of tests made on each group are given as follows :

Plasma Cortisol Level (ug/dl)

Time	Treated Pigs	Control
0800	1.9	4.8
1200	1.5	3.4
1600	3.2	1.6
2000	2.8	1.9
2400	3.5	2.7
0400	3.2	5.5

Plasma Prolactin Level (ug/ml)

Time	Treated Pigs	Control
0800	1.8	0.5
1200	2.3	3.3
1600	2.8	1.3
2000	2.4	1.2
2400	2.3	1.7
0400	1.5	0.1

The effects of bromocriptine implants on fat stores and plasma concentrations of triglyceride, glucose and insulin are given as follows :

Treatment	Backfat Triglyceride % control	Glucose mg/dl	Insulin uV/ml
Control	100	52 ± 8	99 ± 5	10.8 ± 1.8
Bromocriptine (10 mg/day/pig)	86[3]	27 ± 3[3]	86 ± 3[3]	8.8 ± 0.3

Notes: Backfat thickness was used as an index in determining fat stores. These data were obtained 28 days after treatment of the animals.

Plasma was sampled at 1600, 2000 and 2400 after two weeks of treatment. Each pig of the treatment group and control group was sampled.

These data clearly show that the bromocriptine implants altered the phase relationships of the circadian rhythms of plasma corticosteriod and prolactin concentrations, and produced changes beneficial to diabetics. The data show that, near sunset, when lipogenesis is normally greatest in pigs, bromocriptine reduced plasma triglyceride concentration by 48%. Since lipid is produced in the liver and transported in the blood to adipose tissue, the triglyceride reduction is further evidence that bromocriptine has an inhibitory effect on fat synthesis and deposition. In addition, although the reduction in plasma insulin concentration was not statistically significant, bromocriptine reduced plasma glucose levels by 13% during the early period of darkness (2000-2400). The reduction in blood glucose, without an increase in blood insulin concentration, can be explained as a decrease in insulin resistance (greater hypoglycemic responsiveness to insulin). Bromocriptine reduced body fat stores by 14% in the 28 day period of treatment.

Further studies were done on humans, these indicating that the symptoms of non insulin depend-dent, or Type II diabetes can be reduced by treatment with bromocriptine. Examples follow.

Example 2

A 50 year old woman, showing the symptoms of diabetes, was daily given bromocriptine tablets (1.25-2.50 mg/day), taken orally, just after awakening. At the beginning of the treatment, blood glucose concentration was shown by routine testing to be near 250 mg/dl. In the weeks following the initial treatment, the patient's glucose levels fell to 180 mg/dl, to 155 mg/dl, to 135 mg/dl, to 97 mg/dl and to 101 mg/dl. Fasting levels below 120 mg/dl are considered normal. Body weight and indices of body fat were also reduced about 12% by the treatment.

Example 3

A 45 year old woman was being treated with a hypoglycemic agent (diabenase) which had reduced the blood glucose of the patient from 250 mg/dl to about 180 mg/dl during one year of treatment. Following daily oral administration of bromocriptine (parlodel, 1.25-2.5 mg/day), the blood glucose level fell dramatically to 80 mg/dl in 2 weeks. Removal of the hypoglycemic agent allowed glucose levels to rise and remain near 100 mg/dl (a normal level) in the succeeding two months. Body weight and fat were reduced about 10% by the bromocriptine treatment.

Example 4

A 55 year old man weighing nearly 300 pounds was known to be a diabetic hut had resisted all previous admonitions for treatment. At the beginning of oral bromocriptine treatment (parlodel, 2.5 mg/day), his plasma glucose concentration averaged near 350 mg/dl. During 2.5 months of bromocriptine treatment, body weight and plasma glucose concentration gradually but continuously decreased. Body weight has dropped 22 pounds and plasma glucose levels decreased to 160 mg/dl.

The data show that metabolic states are regulated at least in part by an interaction of circadian neuroendocrine rhythms. This hypothesis proposes that the daily rhythms of cortisol and prolactin are individual expressions of two separate circadian systems and that the daily injections of these hormones can reset the phase relations of these two systems. Thus, in a hamster model it has been found that the 0-hour relation resets the circadian oscillations into a pattern that maintains the lean, insulin sensitive state and the 12-hour relation permits retention of a pattern that maintains the obese, insulin resistant state. Another important addition of the present study is that the effects of timed injections of a dopamine agonist, or prolactin inhibiting compound, are long lasting. Apparently once reset, the phase relation of the two circadian oscillations tends to maintain

its altered pattern.

Changes in the phase relations of two circadian neuroendocrine oscillations are evidenced by changes in the phase relations of their circadian expressions. This expectation is fulfilled respecting plasma glucocorticosteroid and prolactin rhythms. In several species examined, the phase relations of the two hormone rhythms differ in lean and fat animals.

The phase relation between the circadian rhythm of plasma insulin concentration and the rhythm of lipogenic responsiveness to insulin is shown to differ in lean and fat animals. Whereas the daily interval of lipogenic responsiveness remains near light onset, the phase of the insulin rhythm varies markedly. The peak concentration of insulin, e.g., occurs near light onset in obese female hamsters held on short day-lengths. That is, the daily peaks of the lipogenic stimulus (i.e., insulin) and the lipogenic response to insulin coincide in fat animals and not in lean animals.

The phase relations of both prolactin and insulin rhythms as well as the rhythms of tissue responses to the hormones are important elements in the regulation of lipogenesis. All of these rhythms, then, would be phase adjusted to regulate lipogenesis. Phase adjustment of these and perhaps other rhythms may also account for insulin resistance.

Claims

1. The use of a dopamine agonist in the manufacture of a medicament for the modification and regulation of lipid metabolism in an animal or human, by administration on a timed daily basis in dosage amount and for a period sufficient to modify and reset the neural phase oscillation of the prolactin rhythm of the said animal or human, such that hyperglycemic sensitivity to insulin is improved, fat stores are reduced, and hyperinsulinemia is suppressed and/or hyperglycemia reduced.

2. The use of a dopamine agonist in the manufacture of a medicament for the modification and regulation of lipid metabolism in an animal or human, by administration on a timed daily basis in dosage amount and for a period sufficient to modify and reset the neural phase oscillations of both the prolactin and glucocorticosteroid of the said animal or human, such that hyperglycemic sensitivity to insulin is improved, fat stores are reduced, and hyperinsulinemia is suppressed and/or hyperglycemia reduced.

3. A use as claimed in Claim 1 or 2 in which the timed daily dosages of the dopamine are to be given daily, once a day, over a period ranging from 10 to 90 days, at levels ranging from 3 to 100 micrograms per pound of body weight.

4. A use as claimed in Claim 3 in which the period is 30 to 60 days and the daily dose 3 to 20 micrograms.

5. A use as claimed in any preceding claim in which the dopamine agonist is 6-methyl-8beta-carbobenzyloxy-aminoethyl-10alpha-ergoline ; 1,6-dimethyl-8beta-carbobenzyloxy-aminomethyl-10alpha-ergoline ; an 8-acylaminoergolene ;ergocornine ;9,10-dihydroergocornine ;bromocriptine, or a D-2-halo-6-alkyl-8-substituted ergoline.